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First Total Synthesis of Antitumor Natural Product (+)- and (−)-Pericosine A: Determination of Absolute Stereo Structure†

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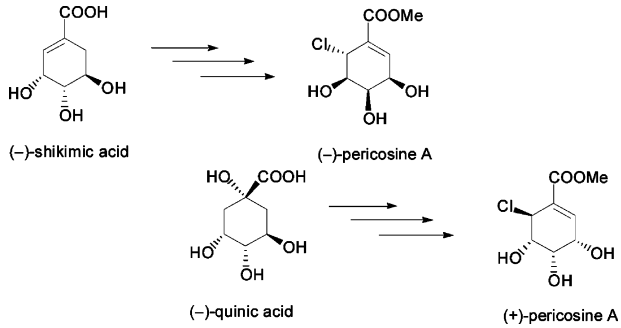

The first total synthesis of (+)- and (−)-pericosine A has been achieved, enabling the revision and determination of the absolute configuration of this antitumor natural product as methyl (3*S*,4*S*,5*S*,6*S*)-6-chloro-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate. Every step of this total synthesis proceeded well with excellent stereoselectivity. Structures of the intermediates in crucial steps were confirmed by detailed 2D NMR analysis.

Introduction

The synthesis of carbasugars has been actively pursued worldwide because of their antiviral, antifungal, and antitumor activities.[1] One recent topic of interest was the total synthesis of the oral anti-influenza drug Tamiflu by two independent groups of Corey and Shibasaki.[2,3] Both groups saw a need to develop a drug to counter the recent emergence of avian flu. Such studies are extremely important in current synthetic organic chemistry and natural product chemistry.[4,5]

The isolation of antitumor natural products pericosines A and B as metabolites of *Periconia byssoides* OUPS-N133 originally separated from the sea hare, *Aplysia kurodai*, was reported in 1997, and their structures (**1** and **2**) are shown in Figure 1.[6] Aside from the significant in vitro cytotoxicity against P388 lymphocytic leukemia cells, pericosine A was reported to have significant in vivo antitumor activity against murine P388 cells. Because of the multifunctionalized cyclohexene structure, these compounds are expected to exhibit various biological activities in addition to antitumor activity. In the course of our synthetic studies of bioactive natural products and their analogues, focusing on small molecules,[7−10] we have been interested in pericosines because of their carbasugar structure.[9,10]

In 1998, Donohoe and co-workers achieved the total synthesis of **2** to elucidate its absolute configuration.[11] However, the absolute configuration of pericosine A had not been elucidated

† This article is dedicated to Professor Yoshimitsu Nagao on the occasion of his retirement from Tokushima University.

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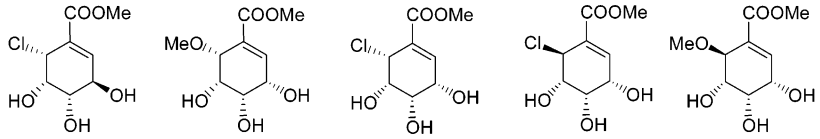

FIGURE 1. Structures of pericosines and related compounds.

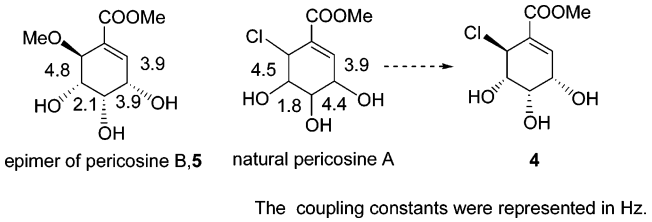

FIGURE 2. Coupling constants in the epimer of perocosine B (**5**) and natural pericosine A.

despite its significant antitumor activity. Our successful asymmetric total synthesis of **1** led us to conclude that the structure of **1** was incorrect.[12] In that synthetic study, we prepared another diastereoisomer (**3**) that was different from pericosine A. Then, elucidation of the true structure of pericosine A became our next task. In a comprehensive review of data related to pericosines,[6,9,10,12] we noted a close similarity between the ^{1}H NMR coupling constants of natural pericosine A[6] and those of the epimer of pericosine B (**5**), which we had reported previously[10] (Figure 2). This led us to deduce that diastereoisomer (**4**) should be natural pericosine A. Described herein is the first total synthesis of (+)- and (−)-pericosine A and the structure revision and determination of the absolute configuration of the antitumor natural product pericosine A in full detail. Part of this work had been reported in a preliminary form.[13]

Results and Discussion

The basic synthetic strategy was almost the same as our previous work on the synthesis of the epimer of pericosine B (**5**), as illustrated in Scheme 1, because our target molecule (**4**) has the same relative configuration. The key reaction attempted at an early stage was the S_Ni-type conversion of the hydroxyl group at C-6 in intermediate (**6**) into Cl atom with retention of configuration. Enol (**6**) could be synthesized from diol (**7** or **8**), which was derived from methyl shikimate derivatives (**9** or **10**), respectively. Both **9** and **10** could be prepared from commercially available (−)-shikimic acid[14] or (−)-quinic acid.[15] Synthetic route A was a path via **7** and **9**, and route B was a path via **8** and **10** in Scheme 1.

As shown in Scheme 2, (−)-quinic acid was converted into diol (**7**) via **9**, as in our previous report.[10] When **7** was treated with excess acetic anhydride, bis-O-acetylated product (**11**) was produced in 51% yield together with desired mono-O-acetylated product (**12**) in 31% yield. The addition of 2.0 equiv of acetic anhydride to **7** afforded only **12** in 85% yield. Acetate **12** was then treated with TBAF to remove the TBS group to give a mixture of undesired **13** in 29% yield and desired **14** in 28% yield with recovery of starting material **12** in 14% yield.

The formation of **13** may proceed via a six-membered boat intermediate, as illustrated in Scheme 3. Or it could be 1,2 then 1,3 migration, all from chair conformation, but 1-O-acetylated intermediate in the 1,2 migration process could not be detected. Diol **14** was oxidized with Dess−Martin periodinane to give β-hydroxyketone (**15**) in 64% yield.

Because the synthesis of **15** described above was not efficient from (−)-quinic acid, alternative route B via **8** and **10** in Scheme 1 was examined.

The synthesis is summarized in Scheme 4. Known methyl shikimate derivative (**16**) prepared from (−)-shikimic acid[16] was oxidized with Dess−Martin periodinane followed by $NaBH_4$ reduction to afford known alcohol (**17**)[17] in an 81% two-step yield. Alcohol **17** was then protected with TBSCl to give silyl ether (**10**) in 69% yield. Dihydroxylation of **10** was carried out with a catalytic amount of OsO_4 and 1.0 equiv of trimethylamine *N*-oxide to give diol (**8**) as a single product in almost quantitative yield. The stereochemistry that assumes a chair conformation was confirmed by analyzing the NOESY spectra of **8**, in which cross-peaks H-2/H-6β and H-3/H-5 were observed. This stereoselectivity was suggested on the basis of Kishi et al.'s rule.[18] Adding 1.0 equiv of acetic anhydride with pyridine to **8** led to the formation of acetate (**18**) in 91% yield. Then, the product was treated with TBAF to give diol (**19**) in 77% yield. Subsequent Dess−Martin oxidation of **19** gave **15** quantitatively. β-Hydroxyketone **15** was dehydrated with TFAA and pyridine to give α,β-unsaturated ketone (**20**) in 76% yield.

Subsequent reduction of **20** with excess $NaBH_4$ in MeOH at −10 °C gave desired product (**21**) in 10% yield with recovery of **10** in 80% yield. The excess hydride species was thought to attack C-2 with leaving of the acetyl group at C-6 and migration of the double bond. When DIBAL was applied as a reducing agent, the desired reaction did not proceed. The best reducing condition was the addition of stoichiometric $NaBH_4$ at −78 °C in dry THF. This condition improved the chemical yield of **21** to 95%.

Then, the stereochemistry of the new stereogenic center at C-3 in **21** was determined as follows. Treatment of **21** with TFA in MeOH at room temperature gave triol (**24**), which was the same as the compound we had previously synthesized as a racemate.[9] Similarly to our previous report, **24** was treated with dimethoxypropane and catalytic TsOH to afford a mixture of acetonides (**25** as the major component and **26** as the minor one), as shown in Scheme 5, and its NOESY spectrum had the following cross-peaks: H-3/H-5, H-3, H-4/one of the acetonide

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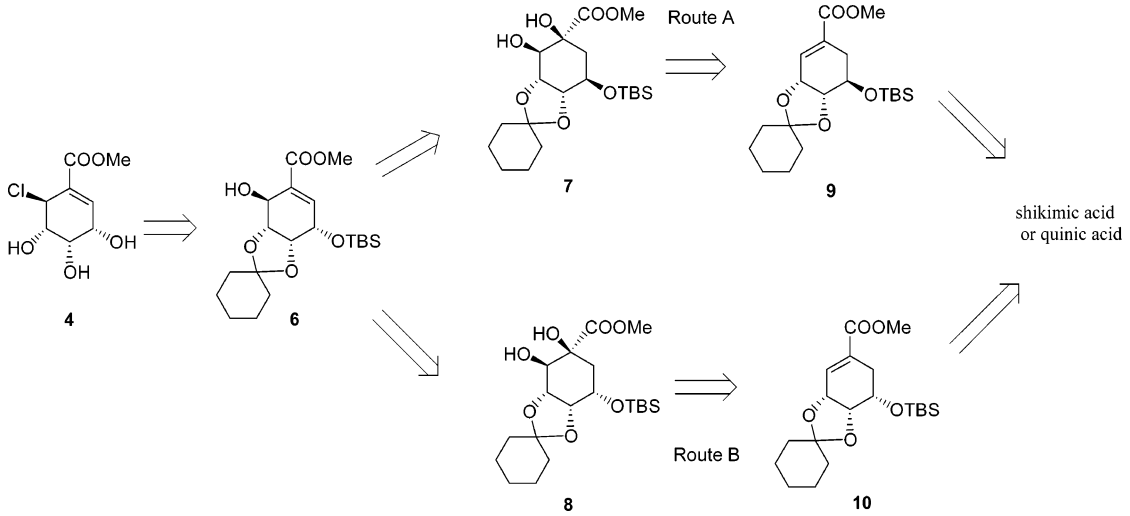
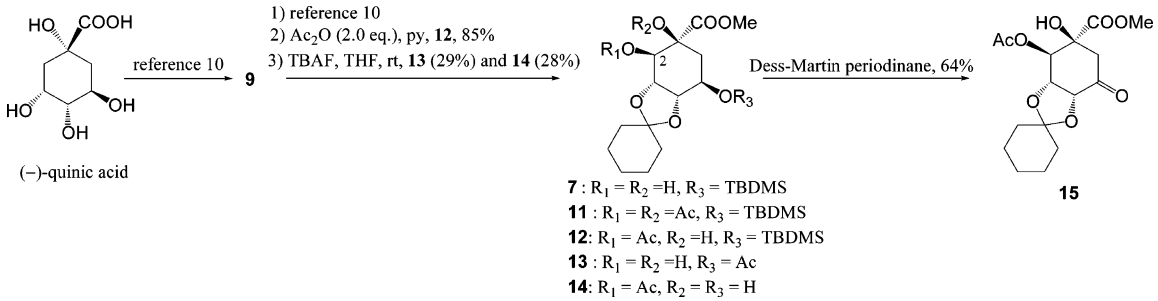
(16) Song, S.; Jiang, S.; Singh, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2833. Of course, **16** could be prepared from inexpensive (−)-quinic acid.
(17) Ulibarri, G.; Nadler, W.; Skrydstrup, T.; Audrain, H.; Chianori, A.; Riche, C.; Grierson, A. A. *J. Org. Chem.* **1995**, *60*, 2753.
(18) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

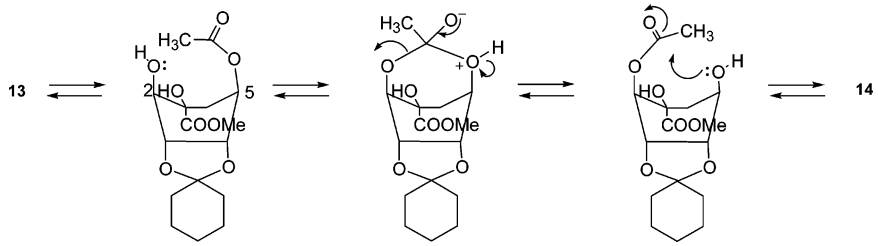
SCHEME 1. Synthetic Strategy of 4



SCHEME 2. Synthetis of 15 from (−)-Quinic Acid via Route A



SCHEME 3. Interconversion between 13 and 14 via Intermediates with Boat Conformation



methyl groups in **25**, and H-4′,H-5′/one of the acetonide methyl groups in **26**.

Subsequent protection of **21** was carried out with careful addition of TBSCl and a stoichiometric amount of imidazole to give desired product **22** in 53% yield. The direct conversion of **18** into **22** was not successful with $SOCl_2$, SO_2Cl_2, $POCl_3$, Martin's sulfurane dehydrating agent,[19] or Burgess reagent.[20] Then, the acetyl group of **22** was removed with K_2CO_3 to give enol (**6**) in 74% yield. At this point, the structure of **6** was confirmed again with detailed 2D NMR experiments. The NOESY cross-peak H-3/H-5 in **6** supported the configuration at C-3 generated by the $NaBH_4$ reduction of **20** to **21** as described above.

The key reaction in this total synthesis of Cl atom introduction was achieved by the addition of excess $SOCl_2$ to **6** in dry CH_2Cl_2 to afford chlorinated product (**23**) in 42% yield. This yield is high compared with the previously reported yield of 10% obtained by the stoichiomeric addition of $SOCl_2$.[13] Other reagents such as AcCl, TsCl, MsCl, or $POCl_3$ did not give **23**. The structure of key intermediate **23** was confirmed by detailed 1D and 2D NMR studies. The assignment of signals of all protons on the cyclohexene ring was based on the ^1H NMR, COSY, and NOESY spectra of **23**. In the NOESY spectra, cross-peaks H-5/*t*-Bu, H-6/*t*-Bu, H-5/SiMe, H-6/SiMe, and H-3,H-4/one of cyclohexyl methylenes were observed. The HMBC cross-peak H-3,H-4/singlet carbon observed at 110.8 ppm of **23** confirmed that the Cl atom was not introduced via an S_Ni mechanism as we had aimed early on, but via an S_N' mechanism with syn selectivity.[21,22] Another plausible mechanism is the [3,3]-sigmatropic rearrangement of chlorosulfonate derived from **6**. However, the S_N' mechanism seemed most likely from the formation of **10** on reduction of **20** with excess $NaBH_4$, as described above. Unfortunately, the stereochemistry at C-6 in **23** could not be determined by NMR analysis at this step but was elucidated later as β-configuration.

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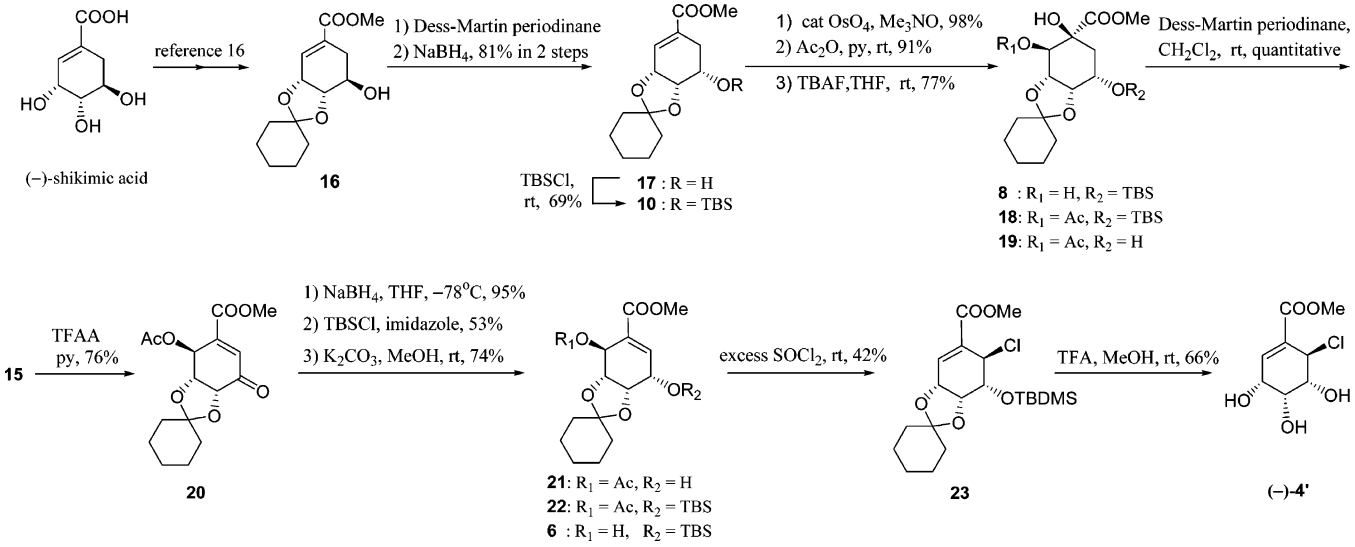
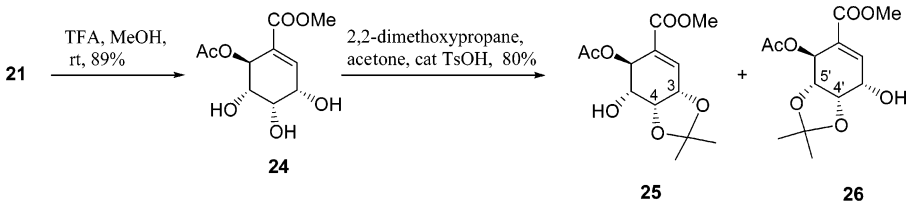
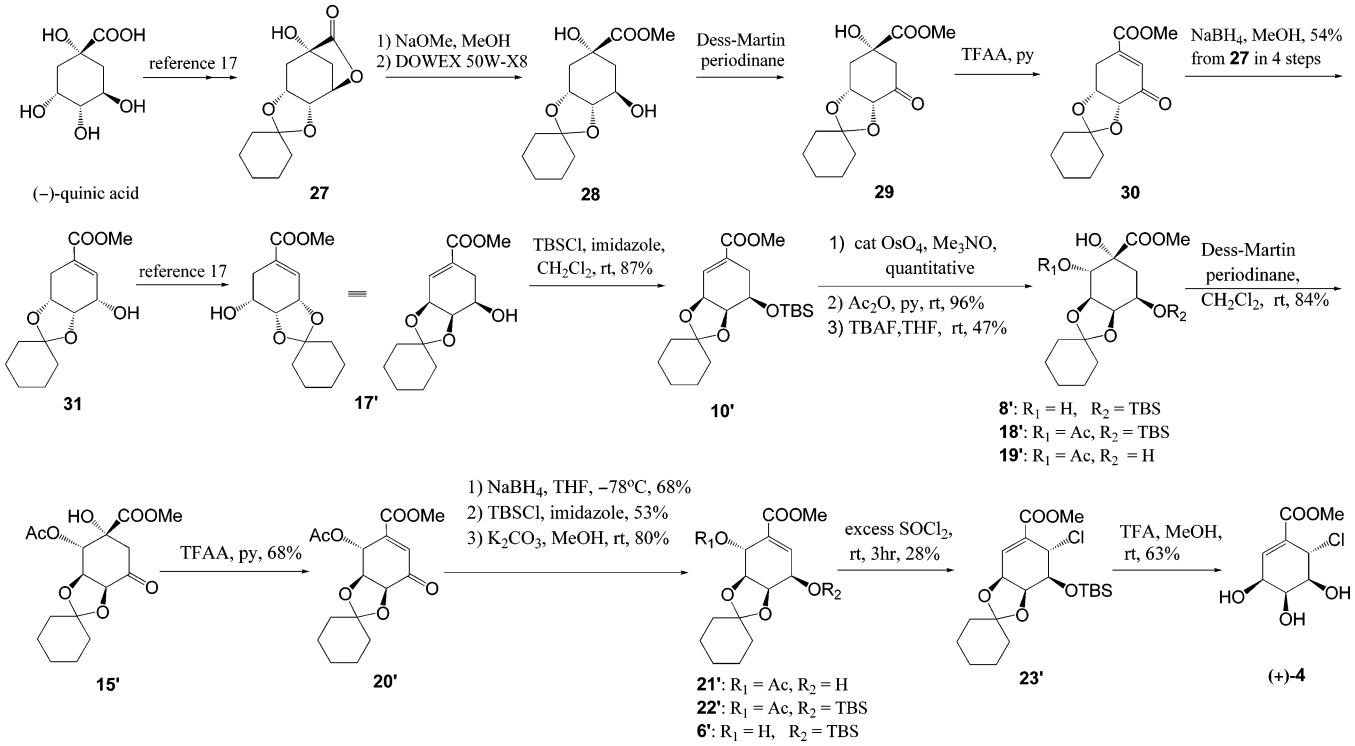
SCHEME 4. Total Synthesis of (−)-4′ from (−)-Shikimic Acid via Route B



SCHEME 5. Confirmation of the Stereochemistry at C-3 in 21



SCHEME 6. Total Synthesis of (+)-4 from Quinic Acid



To complete the total synthesis, **23** was deprotected with TFA to give final product (**4′**) in 66% yield, which was not the all-cis diastereoisomer (**3**) we synthesized previously[12] but pericosine A. This result proved the stereochemistry at C-6 in **23**. Except for the sign of the specific rotation, all the spectral data and the HPLC retention time agreed with those of natural pericosine A. Hence, the total synthesis of the antipode of natural pericosine A was completed, and the absolute configuration of natural pericosine A was assigned as methyl (3*S*,4*S*,5*S*,6*S*)-6-chloro-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate.

Next, the total synthesis of natural pericosine A (**4**) was examined. Since antipode **17′** could be prepared from (−)-quinic

acid,[17] **4** should be synthesized with a similar strategy, as illustrated in Scheme 1.

The synthesis of **4** is shown in Scheme 6. Commercially available (−)-quinic acid was converted into alcohol (**17′**) according to the literature with some modifications. Lactone (**27**) derived from (−)-quinic acid was treated with NaOMe followed by neutralization with DOWEX 50W-X8 to give crude diol (**28**), which was oxidized to β-hydroxyketone (**29**), and **29** was dehydrated with TFAA to enone (**30**) without purification. Then **30** was reduced with $NaBH_4$ to afford enol (**31**) in 54% overall yield from **27**. Enol (**31**) was converted into **17′** as described in the literature.[17] Then, the following transformations of **17′** into **4** were accomplished as above. Since all the spectral data of synthesized (+)-**4** including the specific rotation and the HPLC retention time agreed with the data of natural pericosine A, the first synthesis of natural pericosine A was completed.

Conclusion

We have accomplished the first total synthesis of (+)- and (−)-pericosine A (**4**, **4′**). Every important step in this synthesis proceeded with excellent stereoselectivity. From this total synthesis, the structure of antitumor natural product pericosine A was revised with elucidation of the absolute configuration as methyl (3*S*,4*S*,5*S*,6*S*)-6-chloro-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate.

Experimental Section

Methyl (1*S*,2*R*,3*S*,4*R*,5*R*)-1,2-Bis-*O*-acetyl-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 11. Methyl (1*S*,2*R*,3*S*,4*R*,5*R*)-2-*O*-Acetyl-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 12. A. A mixture of **7** (214.6 mg), acetic anhydride (1 mL, excess), and pyridine (1 mL) was stirred at room temperature for 26 h. Then, the reaction mixture was treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **11** (85.4 mg, 51%) and **12** (121.2 mg, 33%).

B. A mixture of **7** (160.0 mg), acetic anhydride (72.7 μL, 2 equiv), and pyridine (1 mL) was stirred at room temperature for 3 h. A treatment similar to that described above led to the isolation of **12** (149.8 mg, 85%).

11: Oil; $[\alpha]^{22}_D$ +74.7 (*c* 4.7, CH_3Cl); IR (KBr) ν_{max} 1753 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (3H, s, SiMe), 0.10 (3H, s, SiMe), 0.89 (9H, s, *t*Bu), 1.25−1.72 (10H, m), 2.07 (3H, s, CH_3-CO), 2.10 (3H, s, CH_3CO), 2.54 (1H, dd, J = 15.6, 4.8 Hz, H-6_A), 2.62 (1H, ddd, J = 15.6, 4.6, 1.1 Hz, H-6_B), 3.67 (3H, s, COOMe), 4.16 (1H, ddd, J = 5.5, 3.0, 1.1 Hz, H-4), 4.30 (1H, ddd, J = 4.8, 4.6, 3.0 Hz, H-5), 4.46 (1H, dd, J = 8.7, 5.5 Hz, H-3), 5.06 (1H, d, J = 8.7 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ −5.2 (q), −5.0 (q), 18.4 (s), 20.8 (q), 21.4 (q), 23.7 (t), 23.9 (t), 24.9 (t), 25.8 (q), 33.3 (t), 35.1 (t), 37.5 (t), 52.8 (q), 67.7 (d), 73.1 (d), 73.8 (t), 79.1 (d), 79.7 (s), 109.9 (s), 168.9 (s), 169.8 (s), 170.3 (s); HRMS *m*/*z* calcd for $C_{24}H_{40}O_9Si$ $(M)^+$, 500.2439; found, 500.2429.

12: Oil; $[\alpha]^{22}_D$ +49.9 (*c* 2.3, CH_3Cl); IR (liquid film) ν_{max} 3452 (OH), 1746 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (3H, s, SiMe), 0.15 (3H, s, SiMe), 0.91 (9H, s, *t*Bu), 1.20−1.80 (10H, m), 1.99 (1H, ddd, J = 14.8, 5.0, 1.1 Hz, H-6_A), 2.11 (3H, s, CH_3CO), 2.41 (1H, dd, J = 14.8, 3.9 Hz, H-6_B), 3.73 (3H, s, COOMe), 4.19 (1H, m), 4.39 (2H, m), 5.23 (1H, d, J = 8.4 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ −5.0 (q), −4.9 (q), 18.0 (s), 21.0 (q), 23.8 (t), 24.0 (t), 25.0 (t), 25.7 (q), 35.4 (t), 36.0 (t), 37.6 (t), 52.9 (q), 68.8 (d), 74.6 (d), 75.0 (d), 76.4 (s), 78.3 (d), 110.6 (s), 169.9 (s), 172.3 (s); HRMS *m*/*z* calcd for $C_{22}H_{38}O_8Si$ $(M)^+$, 458.2334; found, 458.2336.

Methyl (1*S*,2*R*,3*S*,4*R*,5*R*)-5-*O*-Acetyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 13. Methyl (1*S*,-2*R*,3*S*,4*R*,5*R*)-2-*O*-Acetyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 14. To a THF solution (15 mL) of **12** (103.0 mg) was added 1.0 M TBAF in THF (0.2 mL, 1.0 equiv) at room temperature, and the mixture was stirred overnight. Then, the reaction mixture was treated with aq NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 2% MeOH−CH_2Cl_2) to afford **13** (22.1 mg, 29%) and **14** (21.5 mg, 28%) with recovery of starting material **12** (14.7 mg, 14%). **13:** Oil; $[\alpha]^{22}_D$ +8.6 (*c* 0.12, CH_3Cl); IR (liquid film) ν_{max} 3446 (OH), 1734 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20−1.76 (10 H, m), 1.86 (1H, dd, J = 14.8, 7.0 Hz, H-6_A), 2.09 (3H, s, CH_3CO), 2.49 (1H, dd, J = 14.8, 6.0 Hz, H-6_B), 3.84 (3H, s, COOMe), 3.97 (1H, d, J = 8.0 Hz, H-2), 4.27 (1H, dd, J = 8.0, 6.7 Hz, H-3), 4.34 (1H, t, J = 6.7 Hz, H-4), 5.18 (1H, ddd, J = 7.0, 6.7, 6.0 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 21.2 (q), 23.6 (t), 24.0 (t), 25.0 (t), 34.8 (t), 35.3 (t), 37.6 (t), 53.4 (q), 69.4 (d), 73.7 (d), 76.0 (d), 76.2 (s), 77.2 (d), 110.5 (s), 170.2 (s), 174.5 (s); HRMS *m*/*z* calcd for $C_{16}H_{24}O_8$ $(M)^+$, 344.1470; found, 344.1473. **14:** Oil; $[\alpha]^{22}_D$ +80.9 (*c* 3.8, CH_3Cl); IR (liquid film) ν_{max} 3480 (OH), 1747 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20−1.80 (10H, m), 2.08 (3H, s, CH_3CO), 2.11 (1H, m, H-6_A), 2.43 (1H, dd, J = 14.8, 4.3 Hz, H-6_B), 3.77 (3H, s, COOMe), 4.28 (1H, m, H-5), 4.36 (1H, dd J = 7.8, 5.3 Hz, H-3), 4.38 (1H, m, H-4), 5.19 (1H, d, J = 7.8 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 23.7 (t), 24.1 (t), 25.1 (t), 34.8 (t), 35.3 (t), 37.1 (t), 53.5 (q), 69.4 (d), 73.7 (d), 76.0 (d), 76.2 (s), 77.2 (d), 110.4 (s), 170.1 (s), 174.3 (s); HRMS *m*/*z* calcd for $C_{16}H_{24}O_8$ $(M)^+$, 344.1470; found, 344.1461.

Methyl (1*S*,2*R*,3*S*,4*R*)-2-*O*-Acetyl-3,4-*O*-cyclohexylidene-5-oxo-1,2,3,4-tetrahydroxylcyclohexanecarboxylate 15. To a suspension of Dess−Martin periodinane (93.3 mg, 2.0 equiv) in CH_2Cl_2 (2 mL) was added **14** (38.3 mg) in CH_2Cl_2 (1 mL) at room temperature, and stirring was commenced for 1.5 h. After being diluted with MTBE, the reaction mixture was treated with aq $Na_2S_2O_3$ and aq $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **15** (24.4 mg, 64%). **15:** Oil; $[\alpha]^{22}_D$ +38.8 (*c* 1.8, CH_3Cl); IR (liquid film) ν_{max} 3464 (OH), 1742 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−1.80 (10H, m), 2.12 (3H, s, CH_3CO), 2.66 (1H, dd, J = 16.9, 1.4 Hz, H-6_A), 3.16 (1H, d, J = 16.9 Hz, H-6_B), 3.79 (3H, s, COOMe), 4.56 (1H, dd, J = 6.8, 1.4 Hz, H-4), 4.58 (1H, dd, J = 6.8, 6.2 Hz, H-3), 5.45 (1H, d, J = 6.2 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 20.7 (q), 23.6 (t), 23.8 (t), 24.8 (t), 35.2 (t), 37.0 (t), 45.1 (t), 53.7 (q), 74.9 (d), 76.1 (s), 77.4 (d), 77.4 (t), 112.5 (s), 169.4 (s), 171.8 (s), 201.7 (s); HRMS *m*/*z* calcd for $C_{16}H_{22}O_8$ $(M)^+$, 342.1313; found, 342.1314.

Methyl (3*R*,4*R*,5*S*)-3,4-*O*-Cyclohexylidene-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate 17. To a suspension of Dess−Martin periodinane (7.34 g, 1.1 equiv) in CH_2Cl_2 (8 mL) was added **16** (4.25 g, 15.9 mmol) in CH_2Cl_2 (2 mL) at room temperature, and stirring was commenced for 2 h. After being diluted with MTBE, the reaction mixture was treated with aq $Na_2S_2O_3$ and aq $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a crude ketone (4.15 g). To a suspension of $NaBH_4$ (0.60 g, 4.0 equiv based on **16**) in MeOH (10 mL) was added a solution of crude ketone in MeOH (10 mL) at 0 °C. After being stirred for 1.5 h, the reaction mixture was quenched with aq NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give crude residue, which was purified by silica gel column chromatography (eluent: 3% MeOH−CH_2Cl_2) to give pure **17** (3.40 g, 81% in two steps).

Methyl (3*R*,4*R*,5*S*)-5-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate 10. To a CH_2Cl_2 solution (5 mL) of **17** (775.5 mg) were added TBSCl (547.9 mg, 1.2 equiv), imidazole (393.5 mg, 2.0 equiv), and a catalytic amount of DMAP at room temperature. After being stirred overnight, the reaction mixture was treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **10** (802.7 mg, 69%). **10:** Oil; $[\alpha]^{22}_D$ −11.5 (*c* 2.1, MeOH); IR (KBr) ν_{max} 1723 (C═O), 1652, 1436 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.115 (3H, s, SiMe), 0.118 (3H, s, SiMe), 0.87 (9H, s, *t*Bu), 1.20−1.70 (10H, m), 2.50 (2H, m, H-6_A, 6_B), 3.77 (3H, s, COOMe), 3.92 (1H, ddd, J = 9.8, 5.8, 2.1 Hz, H-3), 4.31 (1H, br d, J = 5.8 Hz, H-4), 4.67 (1H, m, H-5), 6.66 (1H, m, H-2); ^{13}C NMR ($CDCl_3$) δ −4.6 (q), −4.4 (q), 18.3 (s), 23.8 (t), 24.0 (t), 25.0 (t), 25.9 (q), 27.8 (t), 36.0 (t), 37.4 (t), 52.0 (q), 68.8 (d), 73.4 (d), 76.0 (d), 110.6 (s), 129.2 (s), 135.4 (d), 167.0 (s); HRMS *m*/*z* calcd for $C_{20}H_{34}O_5Si$ $(M)^+$, 382.2173; found, 382.2176.

Methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-5-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 8. Olefin (**10**) (1.30 g, 3.4 mmol) was dissolved in 10 mL of solvent (*t*-BuOH/py/H_2O = 20:5:1). OsO_4 (100 mg, cat. amount) and trimethylamine oxide (380 mg, 1.0 equiv) were added to the solution at room temperature, and the reaction mixture was refluxed for 3 h. After cooling, EtOAc (50 mL) and a small amount of saturated aq $Na_2S_2O_3$ were added to the reaction mixture, and this was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 2% MeOH−CH_2Cl_2) to afford **8** (1.40 g, 98%). **8:** Colorless crystals (CH_2Cl_2); mp 158−161 °C; $[\alpha]^{22}_D$ −16.3 (*c* 3.0, MeOH); IR (KBr) ν_{max} 3474 (OH), 1729 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.09 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.91 (9H, s, *t*Bu), 1.36−1.81 (10H, m), 1.83 (1H, dd, J = 13.5, 4.6 Hz, H-6_A), 2.27 (1H, dd, J = 13.5, 10.8 Hz, H-6_B), 3.82 (3H, s, COOMe), 3.98 (1H, d, J = 7.6 Hz, H-2), 4.01 (1H, dd, J = 7.6, 4.8 Hz, H-3), 4.26 (1H, dd, J = 4.8, 4.3 Hz, H-4), 4.34 (1H, ddd, J = 10.5 4.6, 4.3 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.6 (q), 18.2 (s), 23.6 (t), 24.0 (t), 25.7 (t), 25.8 (q), 35.2 (t), 37.0 (t), 38.0 (t), 53.3 (q), 65.9 (d), 74.3 (d), 76.3 (d), 76.9 (s), 79.1 (d), 110.4 (s), 174.6 (s); HRMS *m*/*z* calcd for $C_{20}H_{36}O_7Si$ $(M)^+$, 416.2228; found, 416.2227.

Methyl (1*S*,2*R*,3*S*,4*R*,5*S*)-2-*O*-Acetyl-5-*O*-*tert*-butyldimethyl silyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 18. To a solution of **8** (203.8 mg) in CH_2Cl_2 (2 mL) were added acetic anhydride (50 μL, 1.1 equiv), pyridine (1.0 mL), and a catalytic amount of DMAP at room temperature. After being stirred overnight, the reaction mixture was treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to give **18** (203.6 mg, 91%). **18:** Oil; $[\alpha]^{22}_D$ −10.4 (*c* 0.76, MeOH); IR (liquid film) ν_{max} 3484 (OH), 1750 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.91 (9H, s, *t*Bu), 1.30−1.80 (10H, m), 1.86 (1H, ddd, J = 13.3, 4.8, 1.0 Hz, H-6_A), 2.06 (3H, s, CH_3CO), 2.43 (1H, dd, J = 13.3, 11.4 Hz, H-6_B), 3.73 (3H, s, COOMe), 4.18 (1H, dd, J = 7.8, 4.8 Hz, H-3), 4.30 (1H, ddd, J = 4.8, 3.9, 1.0 Hz, H-4), 4.36 (1H, ddd, J = 11.4 4.8, 3.9 Hz, H-5), 5.24 (1H, d, J = 7.8 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ −4.7 (q), −4.6 (q), 18.2 (s), 20.8 (q), 23.6 (t), 23.9 (t), 25.0 (t), 25.8 (q), 35.4 (t), 36.0 (t), 37.6 (t), 53.3 (q), 65.2 (d), 75.1 (d), 75.7 (s), 76.4 (d), 76.4 (d), 110.6 (s), 169.7 (s), 173.7 (s); HRMS *m*/*z* calcd for $C_{22}H_{38}O_8Si$ $(M)^+$, 458.2333; found, 458.2339.

Methyl (1*S*,2*R*,3*S*,4*S*,5*S*)-2-*O*-Acetyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 19. To a THF solution (2 mL) of **18** (143.0 mg, 0.31 mmol) was added 1.0 M TBAF in THF (0.31 mL, 1.0 equiv) at room temperature, and the mixture was stirred overnight. The reaction mixture was treated with aq NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 2% MeOH−CH_2Cl_2) to afford **19** (82.4 mg, 77%). **19:** Oil; $[\alpha]^{22}_D$ −12.3 (*c* 2.4, MeOH); IR (liquid film) ν_{max} 3478 (OH), 1747 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−1.85 (10H, m), 2.06 (1H, ddd, J = 13.5, 5.2, 0.9 Hz, H-6_A), 2.07 (3H, s, CH_3CO), 2.28 (1H, dd, J = 13.5, 11.2 Hz, H-6_B), 3.75 (3H, s, COOMe), 4.26 (1H, dd, J = 7.8, 4.8 Hz, H-3), 4.30 (1H, br ddd, J = 11.2, 5.2, 4.1 Hz, H-5), 4.45 (1H, br dd, J = 4.8, 4.1 Hz, H-4), 5.24 (1H, d, J = 7.6 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 20.8 (q), 23.7 (t), 23.9 (t), 24.9 (t), 35.4 (q), 36.0 (t), 37.5 (t), 53.4 (q), 65.0 (d), 75.1 (d), 75.7 (d), 76.4 (d), 110.8 (s), 169.7 (s), 173.4 (s); HRMS *m*/*z* calcd for $C_{16}H_{24}O_8$ $(M)^+$, 344.1469; found, 344.1475.

Synthesis of Hydroxyketone 15 from Diol 19. To a suspension of Dess−Martin periodinane (262.2 mg, 2.0 equiv) in 5 mL of CH_2Cl_2 was added **19** (105.4 mg) in CH_2Cl_2 (1 mL) at room temperature, and stirring was commenced for 1 h. After being diluted with MTBE, the reaction mixture was treated with aq $Na_2S_2O_3$ and aq $NaHCO_3$. The organic layer was washed with brine, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **15** (104.6 mg, 100%).

Methyl (4*R*,5*R*,6*S*)-6-*O*-Acetyl-4,5-*O*-cyclohexylidene-4,5,6-trihydroxy-3-oxo-1-cyclohexene-1-carboxylate 20. To a CH_2Cl_2 solution (10 mL) of **15** (3.06 g) were added TFAA (2.5 mL, 2.0 equiv) and pyridine (4 mL) at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **20** (2.21 g, 76%). **20:** Pale yellow oil; $[\alpha]^{22}_D$ +40.2 (*c* 0.99, CH_3Cl); IR (liquid film) ν_{max} 1750 (C═O), 1734 (C═O), 1698 (C═O), 1654 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35−1.80 (10H, m), 2.09 (3H, s, CH_3CO), 3.88 (3H, s, COOMe), 4.43 (1H, d, J = 5.3 Hz, H-4), 4.55 (1H, dd, J = 5.3, 2.1 Hz, H-5), 6.15 (1H, d, J = 2.1 Hz, H-6), 6.96 (1H, s, H-2); ^{13}C NMR ($CDCl_3$) δ 20.7 (q), 23.6 (t), 23.7 (t), 24. 8 (t), 35.0 (t), 37.0 (t), 53.1 (q), 64.1 (d), 73.5 (d), 75.0 (d), 111.5 (s), 134.4 (d), 141.0 (s), 164.9 (s), 169.3 (s), 196.0 (s); HRMS *m*/*z* calcd for $C_{16}H_{20}O_7$ $(M)^+$, 324.1207; found, 324.1206.

Methyl (3*S*,4*S*,5*R*,6*S*)-6-*O*-Acetyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 21. To a suspension of $NaBH_4$ (15.1 mg, 1.05 equiv) in dry THF (10 mL) was added dropwise **20** (470.2 mg) in THF (3 mL) at −78 °C. After being stirred for 1 h, the reaction mixture was treated with aq NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **21** (424.0 mg, 95%) together with **10** (12.6 mg, 3%). **21:** Oil; $[\alpha]^{22}_D$ +53.4 (*c* 3.5, MeOH); IR (liquid film) ν_{max} 3477 (OH), 1739 (C═O), 1733 (C═O), 1653 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20−1.80 (10H, m), 2.01 (3H, s, CH_3CO), 3.03 (1H, d, J = 10.6 Hz, 3-OH), 3.80 (3H, s, COOMe), 4.48 (1H, ddd, J = 10.6, 4.8, 2.0 Hz, H-3), 4.56 (1H, dd, J = 7.0, 2.2 Hz, H-5), 4.67 (1H, ddd, J = 7.0, 4.8, 1.5 Hz, H-4), 5.84 (1H, ddd, J = 2.2, 1.5 1.1 Hz, H-6), 7.14 (1H, dd J = 2.0, 1.1 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ 21.1 (q), 23.8 (t), 24.1 (t), 25.3 (t), 34.1 (t), 35.8 (t), 52.3 (q), 65.4 (d), 66.8 (d), 74.2 (d), 74.8 (d), 109.9 (s), 127.8 (s), 148.2 (d), 164.2 (s), 168.8 (s); HRMS *m*/*z* calcd for $C_{16}H_{22}O_7$ $(M)^+$, 326.1364; found, 326.1366.

Confirmation of the Stereochemistry at C-3 in 21. Enol **21** (6.0 mg) was dissolved in MeOH (1 mL) with TFA (0.1 mL, excess). After being stirred for 30 min at room temperature, the solvent was removed under reduced pressure to give a residue that was purified by preparative TLC (eluent: 5% MeOH−CH_2Cl_2) to

afford **24** (4.0 mg, 89%). Obtained **24** was treated with 2,2-dimethoxypropane (0.1 mL, excess) and catalytic $TsOH·H_2O$ in acetone (0.2 mL) at room temperature for 30 min. The volatile part was removed under reduced pressure to give a crude residue that was then purified by preparative TLC (eluent: 1% MeOH−CH_2Cl_2) to afford a mixture of **25** and **26** in almost 2:1 ratio (overall 3.5 mg, 80%). Spectral data of **24**, **25**, and **26** were identical to those in ref 9.

24: $[\alpha]^{22}_D$ +53.2 (*c* 0.37, MeOH).

Methyl (3*S*,4*R*,5*R*,6*S*)-6-*O*-Acetyl-3-*O*-*tert*-butyldimethylsilyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 22. To a CH_2Cl_2 solution (10 mL) of **21** (424.0 mg, 1.3 mmol) were added TBSCl (234.1 mg, 1.2 equiv) and imidazole (88.5 mg, 1.0 equiv) at room temperature. After being stirred overnight, the reaction mixture was treated with aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 0.5% MeOH−CH_2Cl_2) to afford **22** (303.4 mg, 53%) with recovery of **21** (107.1 mg, 25%). **22:** Oil; $[\alpha]^{22}_D$ +47.5 (*c* 1.1, MeOH); IR (liquid film) ν_{max} 1747 (C═O), 1652 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.16 (6H, s, SiMe), 0.95 (9H, s, *t*Bu), 1.30−1.80 (10H, m), 2.00 (3H, s, CH_3CO), 3.78 (3H, s, COOMe), 4.45 (1H, dd, J = 6.8, 1.6 Hz, H-5), 4.57 (1H, ddd, J = 6.8, 3.8, 1.6 Hz, H-4), 4.67 (1H, dd, J = 3.8, 2.0 Hz, H-3), 5.74 (1H, br t, J = 1.6 Hz, H-6), 7.12 (1H, dt, J = 2.0, 1.6 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ −3.9 (q × 2), 18.8 (s), 21.4 (q), 24.0 (t), 24.2 (t), 25.6 (t), 26.2 (q), 34.1 (t), 36.0 (t), 52.3 (q), 66.5 (d), 68.4 (d), 75.6 (d), 76.7 (d), 109.9 (s), 127.4 (s), 149.6 (d), 164.4 (s), 168.9 (s); HRMS *m*/*z* calcd for $C_{22}H_{36}O_7Si$ $(M)^+$, 440.2227; found, 440.2233.

Methyl (3*S*,4*R*,5*R*,6*S*)-3-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 6. To a MeOH solution (5 mL) of **22** (120.0 mg) was added K_2CO_3 (37.7 mg, 1.0 equiv) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was treated with aq NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to afford **6** (80.0 mg, 74%). **6:** Colorless crystals (CH_2Cl_2); mp 84−86 °C; $[\alpha]^{22}_D$ +14.8 (*c* 1.5, MeOH); IR (KBr) ν_{max} 3436 (OH), 1739 (C═O), 1656 (C═C), 1538 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (6H, s, SiMe), 0.94 (9H, s, *t*Bu), 1.30−1.80 (10H, m), 3.78 (3H, s, COOMe), 4.47 (1H, dd, J = 6.8, 1.9 Hz, H-5), 4.55 (1H, ddd, J = 6.8, 3.8, 1.7 Hz, H-4), 4.71 (1H, m, H-6), 4.76 (1H, dd, J = 3.8, 2.2 Hz, H-3), 7.04 (1H, m, H-2); ^{13}C NMR ($CDCl_3$) δ −4.0 (q), −3.9 (q), 18.7 (s), 24.0 (t), 24.3 (t), 25.4 (t), 26.2 (q), 34.1 (t), 36.1 (t), 52.2 (q), 65.3 (d), 68.1 (d), 76.9 (d), 77.4 (d), 109.4 (s), 130.3 (s), 147. 7 (d), 165.4 (s); HRMS *m*/*z* calcd for $C_{20}H_{34}O_6Si$ $(M)^+$, 398.2123; found, 398.2116.

Methyl (3*R*,4*R*,5*R*,6*R*)-6-Chloro-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate 23. To a dry CH_2Cl_2 solution (2 mL) of **6** (35.0 mg) was added $SOCl_2$ (5 mL, excess) at 0 °C. After being stirred for 3 h, the reaction mixture was poured slowly into ice-cooled aq Na_2CO_3 and extracted three times with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure to give a crude residue that was purified by preparative TLC (eluent: 1% MeOH−CH_2Cl_2) to afford **23** (15.2 mg, 42%). **23:** Colorless oil; $[\alpha]^{22}_D$ −68.5 (*c* 1.5, MeOH); IR (KBr) ν_{max} 1726 (C═O), 1654 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.10 (3H, s, SiMe), 0.13 (3H, s, SiMe), 0.86 (9H, s, *t*Bu), 1.20−1.80 (10H, m), 3.81 (3H, s, COOMe), 4.23 (1H, dd, J = 4.8, 3.4 Hz, H-5), 4.58 (1H, dd, J = 7.1, 3.4 Hz, H-4), 4.72 (1H, dd, J = 7.1, 3.0 Hz, H-3), 4.83 (1H, d, J = 4.8 Hz, H-6), 7.04 (1H, d, J = 3.0 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ −5.2 (q), −4.4 (q), 18.1 (s), 23.7 (t), 23.9 (t), 25.1 (t), 25.7 (q), 34.4 (t), 36.1 (t), 52.3 (q), 53.3 (d), 69.8 (d), 70.5 (d), 72.8 (d), 110.8 (s), 130.2 (s), 138.3 (d), 165.4 (s); HRMS *m*/*z* calcd for $C_{20}H_{33}O_5ClSi$ $(M)^+$, 416.1775; found, 416.1774.

(−)-Pericosine A (4′): Methyl (3*R*,4*R*,5*R*,6*R*)-6-Chloro-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate. Chloride **23** (15.0 mg) was dissolved in MeOH (1.0 mL) and TFA (0.1 mL, excess). After being stirred overnight at 0 °C, the reaction mixture was allowed to return to room temperature and condensed under reduced pressure to afford a crude residue that was purified by RP-HPLC (eluent: 60% MeOH in H_2O, flow rate: 4 mL/min, retention time: 14′ 50″) to give **4′** (5.3 mg, 66%). **4′:** $[\alpha]^{22}_D$ −98.0 (*c* 0.04, EtOH); Oil; IR (liquid film) ν_{max} 3366 (OH), 1725 (C═O), 1653 (C═C) cm^{-1}; ^1H NMR (acetone-d_3) δ 3.80 (3H, s, COOMe), 4.07 (1H, dd, J = 4.4, 1.9 Hz, H-4), 4.12 (1H, dd, J = 4.6, 1.9 Hz, H-5), 4.38 (1H, br dd, J = 4.4, 3.9 Hz, H-3), 4.90 (1H, dd, J = 4.6, 0.8 Hz, H-6), 6.91 (1H, d, J = 3.9 Hz, H-2); ^{13}C NMR (acetone-d_3) δ 52.4 (q), 57.8 (d), 67.1 (d), 68.6 (d), 75.7 (d), 130.5 (s), 141.9 (d), 166.2 (s); HRMS *m*/*z* calcd for $C_8H_{12}O_5{}^{35}Cl$ $(M + H)^+$, 223.0372; found, 223.0370.

Natural Pericosine A: Specific rotation, $[\alpha]^{22}_D$ +104 (*c* 0.04, EtOH) (lit.* $[\alpha]_D$ +57 (*c* 3.16, EtOH));[6] the retention time in RP-HPLC: 32 min (eluent, 50% MeOH in H_2O; flow rate, 4 mL/min) or 14′ 50″ (eluent: 60% MeOH in H_2O, flow rate: 4 mL/min).

Preparation of 31 from 27. Lactone (**27**) (2.58 g) derived from (−)-quinic acid was treated with NaOMe (0.55 g, 1.0 equiv) in MeOH (30 mL) with stirring at room temperature for 3 h. DOWEX 50W-X8 was added carefully to the dark brown reaction mixture until the color changed to pale yellow, and pH was measured using universal pH test paper. When neutralization was completed, the reaction mixture was filtered into a flask, and the solvent was evaporated under reduced pressure to afford crude diol (**28**). To a CH_2Cl_2 solution (20 mL) of **28** was added Dess−Martin periodinane (4.96 g, 1.2 equiv), and the reaction mixture was stirred overnight at room temperature. Usual treatment of the reaction mixture afforded a crude residue of **29**. To a solution of crude **29** in CH_2Cl_2 (30 mL) was added TFAA (1.4 mL, 1.0 equiv) with pyridine (0.82 mL, 1.6 equiv) and catalytic DMAP (100 mg) at 0 °C. After being stirred for 2 h, the reaction mixture was quenched with aq $NaHCO_3$ then neutralized with aq NH_4Cl, then extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give crude **30**. To a suspension of $NaBH_4$ (189.1 mg, 2.0 equiv based on **27**) in MeOH (30 mL) was added a solution of crude **30** in MeOH (10 mL) at 0 °C. After being stirred for 2 h, the reaction mixture was quenched with aq NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered, and evaporated to give crude residue, which was purified by silica gel column chromatography (eluent: 1% MeOH−CH_2Cl_2) to give pure **31** (1.45 g, 54% in four steps). **31:** Oil; ^1H NMR ($CDCl_3$) δ 1.2−1.65 (10H, m), 1.95 (1H, br d, J = 16.4 Hz, H-6_A), 3.04 (1H, dd, J = 16.4, 2.0 Hz, H-6_B), 3.76 (3H, s, COOMe), 4.07 (1H, m), 4.56 (1H, ddd, J = 7.3, 4.8, 1.3 Hz), 4.64 (1H, ddd, J = 7.3, 3.8, 2.4 Hz), 6.93 (1H, m, H-2); ^{13}C NMR ($CDCl_3$) δ 23.9, 24.2, 25.5, 26.8, 34.2, 35.7, 52.0, 68.0, 71.9, 75.5, 109.3, 127.9, 142.0, 165.5.[17]

All ^1H NMR, ^{13}C NMR, IR, and HRMS data for the compounds described below were identical with the data of the antipodes above.

Methyl (3*S*,4*S*,5*R*)-5-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-1-cyclohexane-1-carboxylate 10′. Desired product **10′** (6.39 g) was obtained in 87% yield from **17′** (5.14 g) in the same manner as that for the preparation of **10**. **10′:** $[\alpha]^{22}_D$ +8.6 (*c* 2.0, MeOH).

Methyl (1*R*,2*S*,3*R*,4*S*,5*R*)-5-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 8′. Desired product **8′** (0.66 g) was obtained in 100% yield from **10′** (0.58 g) in the same manner as that for the preparation of **8**. **8′:** $[\alpha]^{22}_D$ +14.5 (*c* 2.0, MeOH).

Methyl (1*R*,2*S*,3*R*,4*S*,5*R*)-2-*O*-Acetyl-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 18′. Desired product **18′** (5.77 g) was obtained in

96% yield from **8′** (5.49 g) in the same manner as that for the preparation of **18**. **18′:** $[\alpha]^{22}_D$ +13.0 (*c* 0.75, MeOH).

Methyl (1*R*,2*S*,3*R*,4*R*,5*R*)-2-*O*-Acetyl-3,4-*O*-cyclohexylidene-1,2,3,4,5-pentahydroxycyclohexanecarboxylate 19′. Desired product **19′** (2.03 g) was obtained in 47% yield from **18′** (5.77 g) in the same manner as that for the preparation of **19**. **19′:** $[\alpha]^{22}_D$ +15.7 (*c* 1.0, MeOH).

Methyl (1*R*,2*S*,3*R*,4*S*)-2-*O*-Acetyl-3,4-*O*-cyclohexylidene-5-oxo-1,2,4-trihydroxy-1-cyclohexenecarboxylate 15′. Desired product **15′** (1.69 g) was obtained in 84% yield from **19′** (2.03 g) in the same manner as that for the preparation of **15**. **15′:** $[\alpha]^{22}_D$ −32.4 (*c* 1.8, MeOH).

Methyl (4*S*,5*S*,6*R*)-6-*O*-Acetyl-4,5-*O*-cyclohexylidene-4,5,6-trihydroxy-3-oxo-1-cyclohexene-1-carboxylate 20′. Desired product **20′** (38.5 mg) was obtained in 68% yield from **15′** (59.9 mg) in the same manner as that for the preparation of **20**. **20′:** $[\alpha]^{22}_D$ −35.6 (*c* 0.99, MeOH).

Methyl (3*R*,4*R*,5*S*,6*R*)-6-*O*-Acetyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 21′. Desired product **21′** (20.9 mg) was obtained in 68% yield from **20′** (30.5 mg) in the same manner as that for the preparation of **21**. **21′:** $[\alpha]^{22}_D$ −54.6 (*c* 2.1, MeOH).

Methyl (3*R*,4*S*,5*S*,6*R*)-6-*O*-Acetyl-3-*O*-*tert*-butyldimethylsilyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 22′. Desired product **22′** (292.7 mg) was obtained in 53% yield from **21′** (410.0 mg) with recovery of **21′** (100 mg, 34%) in the same manner as that for the preparation of **22**. **22′:** $[\alpha]^{22}_D$ −49.0 (*c* 1.1, MeOH).

Methyl (3*R*,4*S*,5*S*,6*R*)-3-*O*-*tert*-Butyldimethylsilyl-4,5-*O*-cyclohexylidene-3,4,5,6-tetrahydroxy-1-cyclohexene-1-carboxylate 6′. Desired product **6′** (212.0 mg) was obtained in 80% yield from **22′** (292.7 mg) in the same manner as that for the preparation of **6**. **6′:** $[\alpha]^{22}_D$ −16.8 (*c* 1.5, MeOH).

Methyl (3*S*,4*S*,5*S*,6*S*)-6-Chloro-5-*O*-*tert*-butyldimethylsilyl-3,4-*O*-cyclohexylidene-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate 23′. Desired product **23′** (25.7 mg, 28%) was obtained from **6′** (87.4 mg) with recovery of **6′** (20.0 mg, 23%) in the same manner as that for the preparation of **23**. **23′:** $[\alpha]^{22}_D$ +73.0 (*c* 2.1, MeOH).

(+)-Pericosine A (4): Methyl (3*S*,4*S*,5*S*,6*S*)-6-Chloro-3,4,5-trihydroxy-1-cyclohexene-1-carboxylate. Desired product **4** (15.0 mg) was obtained in 63% yield from **23′** (44.5 mg) in the same manner as that for the preparation of **4′** and separated by RP-HPLC (eluent: 60% MeOH in H_2O, flow rate: 4 mL/min, retention time: 14′ 50″). **4:** $[\alpha]^{22}_D$ +102.0 (*c* 0.12, EtOH). Natural **4** was applied to the same RP-HPLC conditions (eluent: 60% MeOH in H_2O, flow rate: 4 mL/min) to show the same retention time of 14′ 50″.

Supporting Information Available: General experimental methods and copies of ^{1}H- and ^{13}C-NMR spectra of all new compounds, **31**, (−)-**4′** and (+)-**4**. This material is available free of charge via the Internet at http://pub.acs.org.

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